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(54) **Apparatus for periodically monitoring the composition of a plurality of samples.**

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US-A- 4 108 602

INTERNATIONAL LABORATORY, vol. 11, no. 2, March 1981, pages 92-98, Fairfield, Connecticut, US; H.D. SCHULZE: "Fully automated determination of metal traces directly in flowing sample streams"

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Description

The invention relates to an apparatus for periodically monitoring the composition of a plurality of samples, said apparatus comprising a source of said plurality of samples; a sample vial holder a plurality of sample vials, each said sample vial having an inlet and an outlet conduit for circulating sample fluid from said sample sources therethrough; means for selectively withdrawing sample fluid from each said sample vial; and means for analyzing said withdrawn sample fluid whereby said composition of said sample fluid from said sample source is periodically monitored.

One of the most demanding aspects in many processes, especially manufacturing processes, is the need to acurately determine the composition of a fluid, or a group of fluids, at any given time. Such information is demanded not only in instances where the maintenance of a constant composition is critical, but also in instances where the change, with respect to time, for example, of the composition is critical as well. Some of the better known of these latter processes dissolution analysis of pharmaceuticals; fermentation studies, waste product elements analysis; (such as from sewage treatment plants); and environmental studies.

The dissolution analysis of pharmaceuticals is particularly important not only to protect the general public but also to comply with government regulations. This analysis is performed to ensure proper dosage uniformity. In recent times such an analysis has increased in importance and complexity due to the continuing development of multi-active ingredient medicines as well as the increased use of "time-released" medicines.

Presently, an apparatus required for such dissolution analysis studies is expensive, requires excessive volumes of samples due to the loss of samples during analysis and is frequently inaccurate due to cross-contamination of samples. The conventional apparatus is expensive because of the required fluid conduit systems necessary to supply sequential samples to a translating sample container used during analysis. Presently, most such analyses are carried out using ultraviolet or fluoresence spectrophotometry. This requires a rather complex sample delivery system and is amenable only to single component analysis. Further, since the sample solution, for example one in which a tablet is dissolving, is continually reduced, the results do not represent the true time dissolution in a specific volume. Hence, the measured dosage dissolved is, in fact, inaccurate. Finally, because of the rather complex pumping and valving system required, cross-contamination between samples is a frequent occurence. Such cross-contamination results in inaccuracies in the characterizing of samples. This is a particularly acute problem for a multi-active ingredient medication.

An apparatus as mentioned at the beginning of the description is known from the document, International Laboratory, Volume 11, No. 2, March 1981, pages 92-98, Fairfield, Connecticut, US; H.D. Schulze: "Fully automated determination of metal traces directly in flowing samples streams". In this known apparatus, the sample vial holder can rotate about its own axis and sample vials are arranged on the circumference of the holder around the rotational axis.

It is the object of the invention to improve an apparatus as mentioned at the beginning of the description, in particular, with respect to the use of this apparatus for determining the composition of a fluid, or a group of fluids, at any given time, such as for dissolution analysis.

The apparatus according to the invention is characterized in that the sample vial holder is arranged stationary, and the means for selectively withdrawing sample fluid from each of said sample vials comprises an extracting unit being movable along the plurality of sample vials.

By this inventive solution a much more simple and inexpensive contruction of the apparatus, than in the prior art using movable vials, can be achieved in that no flexible conduits which can follow the movement of the vials has to be provided. Furthermore, according to the displacement of the vials in the prior art device, longer conduits are necessary, increasing the entire fluid volume outside the sample source. In the apparatus according to the invention, a smaller fluid volume outside the sample source and, therefore, a smaller delay time of a fluid volume unit can be achieved. Thus, in the case of a time dependent composition of the sample in the source, there is no great difference between the composition of the fluid in the vial under measure and the actual composition of the fluid in the source.

Other objects and advantages will become apparent to those skilled in the art from the following detailed description read in conjunction with the appended claims and the attached drawings.

Brief Description of the Drawings

The drawings, not drawn to scale, includes:

Figure 1 which is a pictorial view of an apparatus embodying the principles of the present invention,

Figure 2 which is a cross-sectional view of a novel flow-through sample vial useful in the apparatus of Figure 1; and

Figure 3 is a chromatogram of a typical analysis performed by the apparatus of Figure 1.

Detailed Description of the Invention

An apparatus for periodically monitoring the composition of a plurality of samples, generally indicated at 10 in Figure 1 and embodying the principles of the present invention, includes a source 12 of a plurality of samples, a means 14 for accomodating at least one stationary sample vial 16, means 18 for conveying a sample from the source 12 to a sample vial 16 which vial 16 is stationary, means for selectively withdrawing sample fluid from a selected stationary sample vial 16 and means 22 for controlling the sample fluid conveying means 18 and the withdrawing means 20 so that the withdrawing means 20 withdraws sample from a stationary sample vial 16 containing a flowing sample fluid.

In the preferred embodiment, the source 12 of a plurality of samples includes a plurality of sample holders 24 each such sample holder 24 having a stirrer 26, or mixer, associated therewith. Alternatively, the source 12 can be a flowing stream of fluid from which samples can be periodically removed.

The means 14 for accomodating at least one flow-through sample vial 16 can be any sample vial holder mechanism known in the art. However, in the preferred embodiment, where a plurality of stationary sample vials 16 are employed, i.e. one vial 16 to correspond to each sample holder 24, a rack 28 having a base 30 and a vial guide member 32 supported above the base 30 can be employed. In such a rack 28, the sample vials 16 are inserted through openings 34 in the guide member 32 and rest on the base 30. The rack 28 can be stationarily secured by any such means known in the art.

In the preferred embodiment, the conveying means 18 includes a multi-channel pumping mechanism 36. The multi-channel pumping mechanism 36 is best implemented by means of a plurality of peristaltic pumps, which pumps are relatively small and inexpensive. In such an arrangement a large number of different samples can be conveyed from sample holders 24 to stationary sample vials 16 without any danger of cross-contamination.

The means 20 for withdrawing sample fluid from each stationary sample vial 16 includes a translatable sampling probe 38. The position of the probe 38 is controlled by the means 22. Preferrably, the means 22 is a programable dedicated data station or another computer controlled device. As aforestated, the means 22 controls both the conveying means 18 and the withdrawing means 20.

In the preferred application the sampling probe 38 is an injection needle which withdraws a relatively small sample fluid from a vial 16 and delivers it to a liquid chromatograph apparatus, not shown, via which separation and subsequent analysis of the particular sample is performed.

In order to implement the apparatus 10 the stationary sample vial 16 must be a flow-through vial 16. That is, sample fluid delivered thereto via the conveying means 18 must be returned to the respective sampleholder 24. But for the flow-through excessive amounts of sample would be lost. Hence, the periodic monitoring would be inaccurate. Further, the stationary flow-through sample vial must be accessible to the sampling probe 38.

To meet these requirements a unique and novel flow-through vial 16 has been developed to provide the desired features required for the periodic monitoring of dissolving samples. One embodiment of such a vial 16 is shown in Figure 2. Therein is shown a vial body 40 formed from polyethylene, for example, or some equally relatively inert substance. In one embodiment, the body 40 defines a sample volume cavity 42 therein.The cavity 42, in one embodiment, has a diameter of about 6 mm. The body 40 is provided with a cap 44 which retains a (polytetrofluorethylene) PTFE septum 46 thereacross which septum 46 seals the cavity 42 not only against fluid leakage but also from contamination. The body 40 is also provided with an inlet conduit 48 and an outlet conduit 50. In one particular embodiment, the conduits 48 and 50, are stainless steel tubes having gold plating on at least the inside thereof, which gold plating acts to make the stainless steel relatively inert to the particular samples being tested. Preferably, the stainless steel conduits 48 and 50, have a 1,59 mm (1/16 inch) outside diameter and a 1,09 mm (0,043 inch) inside diameter. The stainless steel conduits 48 and 50, are secured to the body by threads formed on the outside thereof and epoxyed in place.

As an alternative a flow-through sample vial 16 can also be formed from a relatively inert glass during the formation of which external input and output connections can also be formed. Alternatively, such a vial 16 can be formed by injection molding techniques using commonly known plastics.

In one particular application of the apparatus 10, the number of stationary flow-through vials 16 is equal to the number of sample holders 24 which is also equal to the number of peristaltic pumps. Each sample holder includes an outlet conduit extending from the holder to the input side of the particular pump dedicated thereto. The output of that pump conveys the fluid via a conduit to the inlet tube of the particular flow-through stationary sample vessel. The output from the flow-through stationary sample vessel is connected back to that same sample holder via a return conduit. Preferably, the inlet conduit exiting the sample holder includes a filter attached thereto, whereby any par-

ticulate matter such as from a partially dissolved medication tablet is prevented from flowing in the conduit and remains in the sample fluid to continue dissolution. The control means is preferably a model LCI-100 which is a Laboratory Computing Integrator marketed by The Perkin-Elmer Corporation, Norwalk, Connecticut and the withdrawing means is an ISS-100 which is an Intelligent Sampling System also marketed by The Perkin-Elmer Corporation, Norwalk, Connecticut.

In one particular analysis, which demonstrates the relatively inexpensive and flexibility and accuracy of the present apparatus. One analgesic tablet was placed in a bath of 900 mm. of 0.1 N of hydrochloric acid. The sample was pumped through a stationary sample vial at the rate of $2\frac{1}{2}$ ml. per minute and was sampled at one injection per minute.

In order to take maximum advantage of the available analytical techniques a short liquid chromatography separating column was used having a bed of carbon 18 bonded silica support. The mobile phase was 18 percent CH_3CN in 1 percent H_3PO_4. The operating conditions where 3.5 ml. per minute, flow rate at a pressure of 2800 lbs. per square inch. using an ultra violet detector at 240 manometers. Such operating conditions require only a 10 microliter volume injection and clearly due to the flow through feature of a sealed vial the sample loss of negligible. As shown therein, the four major components of the tablet were sampled and monitored at 1 minute intervals. It can be seen that the tablet was fully dissolved after about 13 to 15 minutes. If the same test where to be performed under the same conditions and apparatus available to the pharmaceuticalindustry such an analysis would require on the order of about 5-10 hours.

In an actual analysis one of the sample holders 24, or more conveniently a vial which may or may not be a flow-through type, will contain a standard solution to provide a baseline measurement. Such a baseline measurement is desireable in order to monitor other elements of the analytical system, such as a separating column.

From the above discussion, it will be understood that the apparatus described herein is not only relatively inexpensive, simple to operate, in fact it can be fully automated by use of a data station controlled by known microprocessors. The apparatus is also extremely accurate and avoids cross-contamination between a plurality of sample fluids. This advantage is derived from the fact that each sample holder has a single stationary sample vial associated therewith and both simple input conduits and sample output conduits associate therewith.

In a particular application in the pharmaceutical industry it will be understood that more than a single tablet or medication under examination would be simultaneously analyzed. Although Figure 1 indicates that there are six sample holders and consequently six circulating pumps this number can easily be extended without requiring excessive costs or space. In such an instance the withdrawing mechanism could be programmed to sample each vial at one minute intervals as well as provided with means and a data station to separate the data from each subsequent piece of data and rapidly provide the operator with a chromatogram or other form of information demonstrating all necessary parameters to describe the dissolution which takes place.

Claims

1. An apparatus for periodically monitoring the composition of a plurality of samples, said apparatus comprising:

   a source of plurality of samples;

   a sample vial holder (28) having a plurality of sample vials (16), each said sample vial (16) having an inlet (48) and an outlet (50) conduit for circulating sample fluid from said sample sources therethrough;

   means (20) for selectively withdrawing sample fluid from each said sample vial (16); and

   means for analyzing said withdrawn sample fluid whereby said composition of said sample fluid from said sample source is periodically monitored,

   characterized in that

   the sample vial holder (28) is arranged stationary; and the means (20) for selectively withdrawing sample fluid from each of said sample vials comprises an extraction unit being movable along the plurality of sample vials.

2. Apparatus as claimed in Claim 1 wherein said source is a stream of flowing fluid.

3. Apparatus as claimed in Claim 2 further comprising:

   means for conveying fluid from said stream through said flow-through sample vials.

4. Apparatus as claimed in Claim 3 further comprising:

   means for controlling said fluid conveying means and said sample fluid withdrawing

means whereby said withdrawing means is activated only when fluid is flowing through said sample vial via said conveying means.

5. Apparatus as claimed in Claim 1 wherein said source is a plurality of sample holders.

6. Apparatus as claimed in Claim 5 further comprising:

means for conveying sample fluid from a selected sample holder through a sample vial associated therewith.

7. Apparatus is claimed in Claim 6 wherein said sample fluid conveying means includes a plurality of peristaltic pumps.

8. Apparatus as claimed in Claim 5 further comprising:

means for controlling said selective withdrawing means whereby said withdrawing means withdraws fluid from said sample vial associated with said selected sample holder.

Revendications

1. Dispositif pour le contrôle périodique de la composition d'une pluralité d'échantillons, ledit dispositif comprenant :

une source de pluralité d'échantillons ;

un support de flacon d'échantillon (28) possédant une pluralité de flacons d'échantillon (16) chaque dit flacon d'échantillon (16) ayant un conduit d'entrée (48) et de sortie (50) pour le fluide échantillon circulant à travers lui depuis lesdites sources d'échantillon ;

des moyens (20) pour prélever sélectivement un fluide échantillon à partir de chaque dit flacon d'échantillon (16) ; et

des moyens pour analyser ledit fluide échantillon prélevé de façon à ce que ladite composition dudit fluide échantillon issu de ladite source d'échantillon soit périodiquement contrôlée,

caractérisé en ce que

le support de flacon d'échantillon (28) est disposé de façon fixe ; et les moyens (20) pour prélever sélectivement un fluide échantillon à partir de chacun desdits flacons d'échantillon comprennent une unité d'extraction qui est mobile le long de la pluralité des flacons d'échantillon.

2. Dispositif selon la revendication 1 dans lequel ladite source est un courant de fluide en circulation.

3. Dispositif selon la revendication 2 comprenant de plus :

des moyens pour transporter le fluide depuis ledit courant à travers ledit flacon d'échantillon à écoulement transversal.

4. Dispositif selon la revendication 3 comprenant en outre :

des moyens pour contrôler lesdits moyens de transport de fluide et lesdits moyens de prélèvement de fluide échantillon de façon à ce que lesdits moyens de prélèvement soient mis en fonctionnement seulement lorsque le fluide circule à travers ledit flacon d'échantillon via lesdits moyens de transport.

5. Dispositif selon la revendication 1 dans lequel ladite source est une pluralité de supports d'échantillon.

6. Dispositif selon la revendication 5 comprenant en outre :

des moyens pour transporter le fluide échantillon depuis un support d'échantillon choisi à travers le flacon d'échantillon qui lui est associé.

7. Dispositif selon la revendication 6 dans lequel lesdits moyens de transport du fluide échantillon incluent une pluralité de pompes péristaltiques.

8. Dispositif selon la revendication 5 comprenant de plus :

des moyens pour contrôler lesdits moyens de prélèvement sélectif de façon que lesdits moyens de prélèvement prélèvent du fluide à partir dudit flacon d'échantillon associé avec ledit support d'échantillon choisi.

Patentansprüche

1. Eine Vorrichtung zum periodischen Überwachen der Zusammensetzung einer Vielzahl von Proben, wobei die Vorrichtung umfaßt:

eine Quelle einer Vielzahl von Proben;

einen Probenflaschenhalter (28) mit einer Vielzahl von Flaschen (16), wobei jede Probenflasche (16) eine Einlaß- (48) und eine Auslaßleitung (50) für die Zirkulation einer Probenflüssigkeit aus den Probenquellen durch die Flasche hindurch aufweist;

eine Einrichtung (20) zum selektiven Entnehmen von Probenflüssigkeit aus jeder genannten Probenflasche (16); und

eine Einrichtung zum Analysieren der entnommenen Probenflüssigkeit, wodurch die Zusammensetzung der Probenflüssigkeit aus der Probenquelle periodisch überwacht wird,

dadurch gekennzeichnet,

daß der Probenflaschenhalter (28) stationär angeordnet ist; und daß die Einrichtung (20) zum selektiven Entnehmen von Probenflüssigkeit aus jeder der Probenflaschen eine Extraktionseinheit umfaßt, die längs der Vielzahl von Probenflaschen bewegbar ist.

2. Eine Vorrichtung nach Anspruch 1, wobei die Quelle ein Strom eines strömenden Fluids ist.

3. Vorrichtung nach Anspruch 2, welche ferner umfaßt:

eine Einrichtung zum Fördern von Flüssigkeit aus dem Strom durch die Durchflußprobenflaschen hindurch.

4. Vorrichtung nach Anspruch 3, welche ferner umfaßt:

eine Einrichtung zum Steuern der Fluidförderungseinrichtung und der Einrichtung zum Entnehmen des Probenfluides, wobei die Entnahmeeinrichtung nur aktiviert wird, wenn Fluid durch die Probenflasche über die Fördereinrichtung strömt.

5. Vorrichtung nach Anspruch 1, wobei die Quelle eine Vielzahl von Probenhaltern umfaßt.

6. Vorrichtung nach Anspruch 5, welche ferner umfaßt:

eine Einrichtung zum Fördern von Probenflüssigkeit aus einem ausgewählten Probenhalter durch die damit verbundene Probenflasche.

7. Vorrichtung nach Anspruch 6, wobei die Probenflüssigkeitsfördereinrichtung eine Vielzahl von peristaltischen Pumpen enthält.

8. Vorrichtung nach Anspruch 5, welche ferner umfaßt:

eine Einrichtung zum Steuern der Einrichtung für die selektive Entnahme, wobei die Entnahmeeinrichtung Flüssigkeit aus der Probeflasche, die dem ausgewählten Probenhalter zugehörig ist, entnimmt.

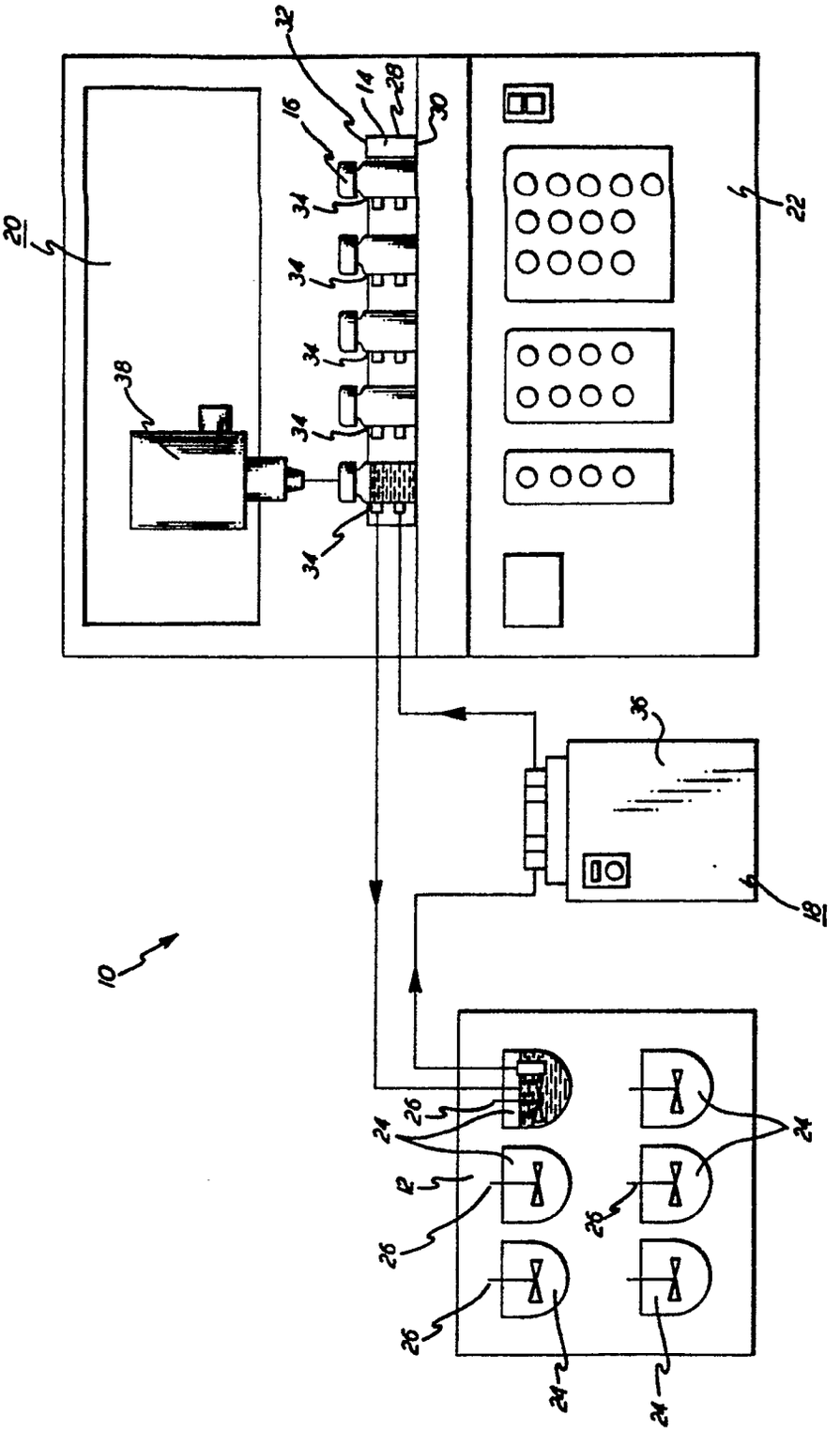
32
14
28
30
16
34
34
34
34
34
38
20
22
36
18
10
24
26
12
26
26
24
24
24
26

FIG. 1

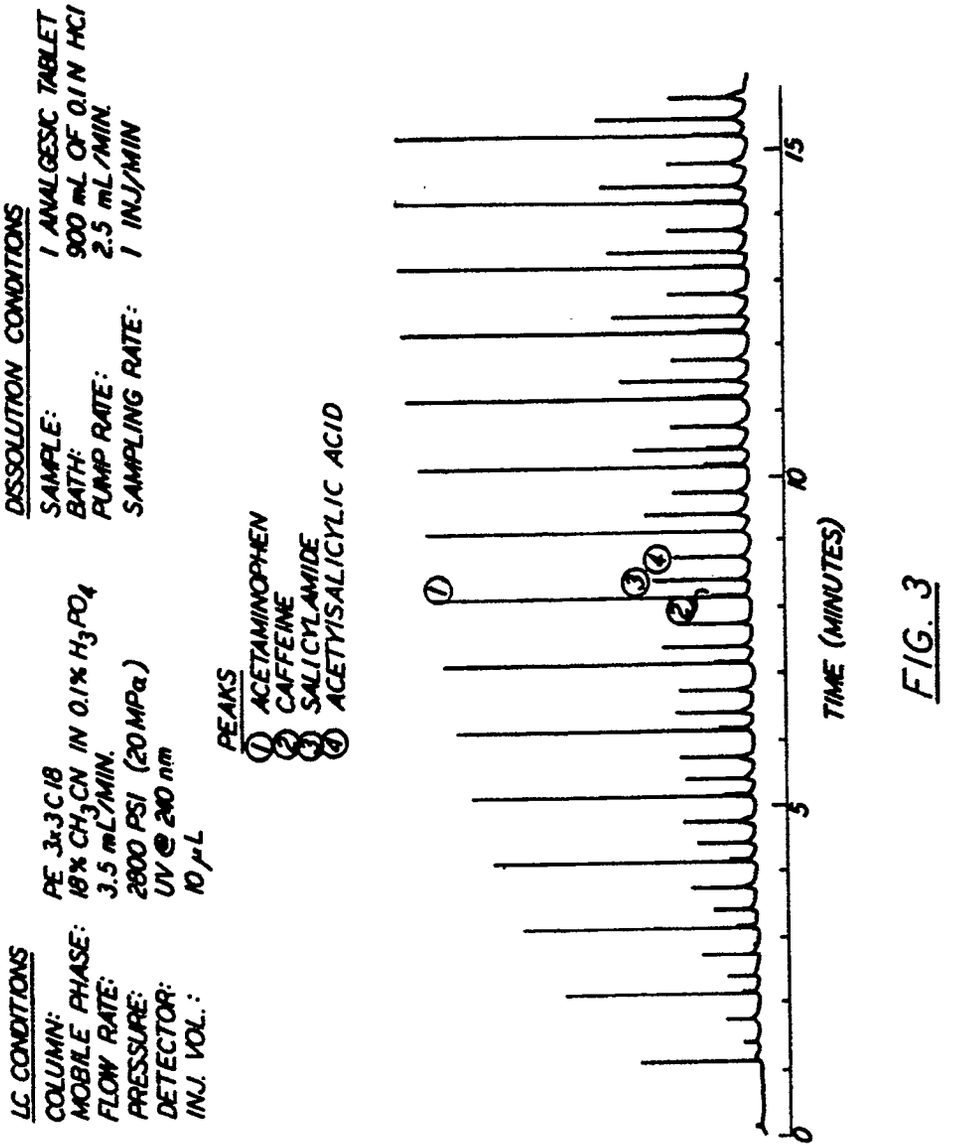
LC CONDITIONS
COLUMN: PE 3x3 C18
MOBILE PHASE: 18% CH_3CN IN 0.1% H_3PO_4
FLOW RATE: 3.5 mL/MIN.
PRESSURE: 2800 PSI (20 MPa)
DETECTOR: UV @ 240 nm
INJ. VOL.: 10 µL
DISSOLUTION CONDITIONS
SAMPLE: 1 ANALGESIC TABLET
BATH: 900 mL OF 0.1 N HCl
PUMP RATE: 2.5 mL/MIN.
SAMPLING RATE: 1 INJ/MIN
PEAKS
① ACETAMINOPHEN
② CAFFEINE
③ SALICYLAMIDE
④ ACETYISALICYLIC ACID
0
5
10
15
TIME (MINUTES)

FIG. 3

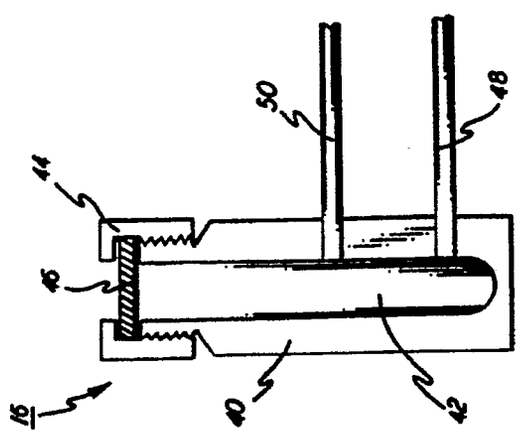
15
40
42
44
46
48
50

FIG. 2